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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/578,530 | 02/01/2007 | Sergei Gryaznov | 074/002 | 5144 |

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| EXAMINER | |
|---|---|
| ZARA, JANE J | |
| **ART UNIT** | **PAPER NUMBER** |
| 1635 | |
| **MAIL DATE** | **DELIVERY MODE** |
| 08/25/2010 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/578,530 | GRYAZNOV ET AL. | |
| | Examiner | Art Unit | |
| | Jane Zara | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *24 June 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *42-80* is/are pending in the application.

4a) Of the above claim(s) *52-56 and 65-74* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-51,57-64 and 75-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6-24-10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

This Office action is in response to the communication filed 6-24-10.

Claims 42-80 are pending in the instant application.

### *Election/Restrictions*

This application contains claims 52-56, 65-74, drawn to an invention nonelected with traverse in the reply filed on 8-21-09. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

### *Response to Arguments and Amendments*

Applicant's arguments with respect to claims 42-51, 57-64, 75-80 have been considered but are moot in view of the new ground(s) of rejection set forth below.

*Withdrawn Rejections*

Any rejections not repeated in this Office action are hereby withdrawn.

*Rejections Necessitated by Amendments*

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 42, 44, 50, 51, 79, 80 are rejected under 35 U.S.C. 102(e) as being anticipated by Zinnen (US 2005/0203044).

Zinnen (US 2005/0203044) teaches siRNA comprising 15-25 nucleotides complementary to a target nucleic acid sequence, comprising at least one nucleotide, or optionally up to 80% nucleotides comprising thiophosphoramidate linkages and further comprising a 2'-fluoro or 2'-O-alkyl modifications, which siRNA is optionally single stranded or double stranded, which siRNA inhibits expression of an endogenous mammalian target gene (see entire document, esp. paragraphs 0004, 0012, 0074, 0082, 0087-102).

Claims 42-51, 57-62, 64, 75-80 are rejected under 35 U.S.C. 102(e) as being anticipated by Gryaznov et al (US 2005/0113325).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Gryaznov et al (US 2005/0113325) teach iRNA molecules, including single or double stranded siRNA molecules between 15-25 nucleobases in length, or optionally single stranded and at least 17 nucleobases in length, comprising at least one nucleotide, or optionally comprising 60 or 80% nucleotides comprising ribo-N3' -> P5' thiophosphoramidate linkages and further comprising 2'-fluoro or 2'-O-alkyl modifications, which iRNA has a lipid moiety covalently conjugated to its 5' or 3' terminus, which lipid moiety is optionally a fatty acid, hydrocarbon or sterol, and which iRNA targets and inhibits the expression of a human endogenous target gene (see entire document, esp. paragraphs 0005, 0012, 0013, 0030, 0038, Figure 2, 0058, 0069, 0078, 0097-0107, 0139-0141, 0170-0173, 0201, example 3, claims 12 and 14.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 42-51, 57-64, 75-80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zinnen (US 2005/0203044) and Pruzan et al (Nucl. Acids Res., Vol. 30, No. 2, pages 559-568, 2002), the combination in view of Manoharan et al (US 2005/0164235), Davis (US 2005/0136430), and Jiang et al (US 2006/0116331).

The claims are drawn to iRNA molecules, including single and double stranded siRNA molecules between 15-25 nucleobases in length comprising at least one, or optionally 60-80% nucleotides comprising ribo-N3' -> P5' thiophosphoramidate linkages and 2'-fluoro or 2'-O-alkyl modifications, which iRNA has a lipid moiety covalently conjugated to its 5' or 3' terminus, which lipid moiety is optionally a fatty acid, hydrocarbon or sterol, which fatty acid is optionally substituted with a fluorine, and which iRNA targets and inhibits the expression of a human endogenous target gene or a HIV gene.

Zinnen (US 2005/0203044) teaches siRNA comprising 15-25 nucleotides complementary to a target nucleic acid sequence, comprising at least one nucleotide, or

optionally up to 80% nucleotides comprising thiophosphoramidate linkages and further comprising a 2'-fluoro or 2'-O-alkyl modifications, which siRNA is optionally single stranded or double stranded, which siRNA inhibits expression of an endogenous mammalian or HIV target gene (see entire document, esp. paragraphs 0004, 0012, 0074, 0082, 0087-102).

Pruzan et al (Nucl. Acids Res., Vol. 30, No. 2, pages 559-568, 2002) teach oligonucleotides comprising N3' -> P5' thiophosphoramidate linkages, and further comprising 2'-deoxy ribose rings, as well as teaching that single stranded phosphoramidate containing, oligonucleotides are highly resistant to nuclease degradation, and display high specificity for RNA and DNA targets (see entire document).

The primary references do not teach oligonucleotides comprising conjugated lipids, nor fatty acids substituted with at least one fluorine.

Manoharan et al (US 2005/0164235) teach iRNA molecules, including single or double stranded siRNA molecules between 15-25 nucleobases in length comprising at least one, or optionally all ribo-N3' -> P5' phosphoramidate linkages, and further comprising 2'-fluoro or 2'-O-alkyl modifications, and which iRNA has a lipid moiety covalently conjugated to its 5' or 3' terminus, which lipid moiety is optionally a fatty acid, hydrocarbon or sterol, and which iRNA targets and inhibits the expression of a human endogenous target gene or a HIV gene (see esp. pages 5, 6, 8-11, 22, 23, 35-37, 40, 42, 49, 53-54).

Davis (US 2005/0136430) teach iRNA molecules, including single or double stranded siRNA molecules between 15-25 nucleobases in length comprising at least one, or optionally all ribo-N3' -> P5' phosphoramidate linkages, and further comprising 2'-fluoro or 2'-O-alkyl modifications, and which iRNA targets and inhibit the expression of a human endogenous target gene (see esp. the abstract, pages 3, 5-8, 14-16).

Jiang et al (US 2006/0116331) teach oligonucleotides with covalently conjugated lipid moieties, which lipids comprise fatty acids comprising at least one fluorine, and Jiang teaches the advantages of incorporating fluorines into fatty acids and conjugating them to oligonucleotides for enhancing amphiphilic molecules in their anti-HIV activity (see esp. paragraphs 0023-0035).

It would have been obvious to incorporate the phosphoramidate and thiophosphoroamidate containing oligonucleotides taught by Pruzan and Zinnen into the siRNA molecules taught by Davis and Manoharan for targeting and inhibiting known target genes, as well as for designing therapeutic agents for HIV treatment because these linkages have been used for gene therapy, including for HIV therapy because such oligonucleotides are well known to be nuclease resistant and to bind to target RNA, as taught previously by Pruzan and Zinnen. One would have been motivated to incorporate 2'-fluoro or 2'-alkyl modifications into the nucleotides because these modifications, combined with the modified internucleotide linkages claimed, were well known to provide oligonucleotides with enhance stability and target binding, as taught previously by many in the field, including Davis, Manoharan and Zinnen.

It would have been obvious to conjugate lipids to the oligonucleotides instantly claimed, and to incorporate fluorines into fatty acids of lipid groups that are covalently linked to inhibitory oligonucleotides, including single and double stranded iRNA molecules because Manoharan, Davis and Jiang taught the methods to do this, and it was well known in the art that fluorocarbon group analogs have enhanced anti-HIV capabilities. One would have been motivated to design these fluorine containing inhibitory molecules as a means of enhancing the therapeutic efficacy of iRNA molecules that target HIV in subjects in need of such therapy. One would have reasonably expected that the lipophilicity of inhibitory oligonucleotides would be enhanced by the conjugation of these fatty acid containing lipid moieties, enhancing cellular penetration, and that these oligonucleotides would provide better anti-HIV therapeutic effects because of enhanced cellular uptake and because of their cumulative anti-HIV and HIV inhibitory capacities.

For these reasons, the instant invention would have been obvious to one of skill in the art at the time of filing.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 42-51, 57-64, 75-80 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 2 of U.S. Patent No. 7494982, in view of Gryaznov et al (US 2005/0113325). Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to molecules comprising at least one ribo-N3' -> P5' phosphoramidate or thiophosphoramidate linkage.

Gryaznov et al (US 2005/0113325) teach iRNA molecules, including single and double stranded siRNA molecules between 15-25 nucleobases in length comprising at least one, or optionally all ribo-N3' -> P5' phosphoramidate or thiophosphoramidate linkages, and optionally further comprising 2'-fluoro or 2'-O-alkyl modifications, and which iRNA has a lipid moiety covalently conjugated to its 5' or 3' terminus, which lipid moiety is optionally a fatty acid, hydrocarbon or sterol, which fatty acid is optionally substituted with a fluorine, and which iRNA targets and inhibits the expression of a human endogenous target gene (see entire document, including claims 1-25).

It would have been obvious to incorporate the teachings of Gryaznov of incorporating other well known modifications which provide for enhanced

oligonucleotide stability and target binding into the oligonucleotides of Gryaznov because the technology and advantages to do so were well known in the art. It would also have been obvious to attach lipid moieties because it was well known that lipid moieties enhance target cell uptake, and the technology to conjugate or attach lipids to oligonucleotides was also well known in the art at the time of filing.

### *Conclusion*

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94

(December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is **571-273-8300**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** The examiner's office hours are generally Monday-Friday, 10:30am - 7pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Chris Low, can be reached on (571) 272-0951. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

**Jane Zara**
**8-24-10**

/Jane Zara/

Primary Examiner, Art Unit 1635